CLAIMS

1. A diagnostic method for estimating for a patient the treatment response of a disease caused by a pathogen to a drug, the method comprising:

comparing the fold change resistance value of the pathogen infecting the patient to a clinical cut-off value which is the fold change resistance value at which a clinically relevant variation of clinical response is observed;

wherein the clinical cut-off value is established by modeling the clinical response of a population of patients treated with the drug to the disease caused by the pathogen as a function of the fold change resistance of the pathogen infecting the patients.

2. A method according to claim 1, wherein the cut-off value is determined as a function of treatment response data in treated subjects, considering baseline pathogen load, baseline fold change resistance and baseline activity of coadministered drugs targeted to the pathogen.

3. A method according to claim 1, wherein the cut-off value is calculated by reference to the pathogen load drop.

4. A method according to claim 3, wherein the cut-off value is calculated by reference to the log pathogen load drop.

5. A method according to claim 4, wherein the log pathogen load drop is calculated by performing a linear regression analysis using data from a dataset of treatment response data, wherein the log pathogen load drop $LogPL\ drop_i$, for the pathogen infecting a patient i, is modelled as the sum of all of the individual contributions for factors that influence pathogen load drop, according to the following equation:

$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i) + \varepsilon_i$$

wherein $BaselinePL_i$ represents the pathogen load of the patient measured at the start of treatment by the drug,
PSS_i is a phenotypic sensitivity score representing the number of active drugs in the background treatment regimen for the patient, excluding the drug whose contribution to treatment response is being modelled,
FC_i is a baseline fold change resistance,
β_0 is the intercept,

β_1 is a coefficient representing the increase in log pathogen load drop per unit increase of the log of the $BaselinePL_i$,
β_2 is a coefficient indicating the increase in log pathogen load drop per unit increase of the number of sensitive drugs in the background treatment regimen,
β_3 is a coefficient indicating the increase in log pathogen load drop per unit increase of the inverse of FC_i,

and wherein the error term, ε_i, represents the difference between the modelled prediction and the experimentally determined measurement.

6. A method according to claim 4, wherein the log pathogen load drop is calculated by performing a linear regression analysis using data from a dataset of treatment response data, wherein the log pathogen load drop $LogPL\ drop_i$, for the pathogen infecting a patient i, is modelled as the sum of all of the individual contributions for factors that influence pathogen load drop, according to the following equation:

$$LogPLdrop_i = \beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(cPSS_i) + \beta_3(cPSS_i)^2 + \beta_4(FC_i)^p + \beta_5(H_5) + ... + \beta_n(H_n) + \varepsilon_i$$

wherein the terms of the equation are the same as those given in claim 5, and additionally, p is a power transformation (e.g. ranging from -3 to 1) and H_5 to H_n are treatment history parameters or parameters describing the background therapy as a function of a certain therapeutic class.

7. A method according to claim 1, wherein the cut-off response value is calculated by reference to the probability of the pathogen being susceptible to treatment by the drug for the patient, herein termed *Prob of success*.

8. A method according to claim 7, wherein *Prob of success* is calculated by performing a logistic regression analysis using data from a dataset of treatment response data, wherein *Prob of success* is modelled according to the following equation:

$$Prob\ of\ success = \frac{\exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i))}{(1 + \exp(\beta_0 + \beta_1 Log(BaselinePL_i) + \beta_2(PSS_i) + \beta_3(1/FC_i)))}$$

wherein $BaselinePL_i$ represents the pathogen load of the patient measured at the start of treatment by the drug,

PSS_i is a phenotypic sensitivity score representing the number of active drugs in the background treatment regimen for the patient, excluding the drug whose contribution to treatment response is being modelled,
FC_i is a baseline fold change resistance,
β_0 is the intercept,
β_1 is a coefficient representing the increase in log pathogen load drop per unit increase of the log of the $BaselinePL_i$,
β_2 is a coefficient indicating the increase in log pathogen load drop per unit increase of the number of sensitive drugs in the background treatment regimen, and
β_3 is a coefficient indicating the increase in log pathogen load drop per unit increase of the inverse of FC_i.

9. A method according to claim 1, wherein the cut-off fold change resistance value is calculated by reference to the likelihood of a patient achieving treatment success or failure, where a definition of success is having an undetectable pathogen load after treatment with a particular drug, using a classification tree.

10. A method according to claim 9, wherein the clinical cut-off is defined as the fold change resistance threshold value that makes the best distinction between the population with successful treatments and the population with unsuccessful treatments.

11. A method according to any one of the preceding claims, wherein the baseline fold change resistance is determined by comparing the genotype of the disease causing pathogen to phenotype data collected from a group of patients infected with a pathogen of similar genotype.

12. A method according to claim 11, wherein the baseline fold change resistance is determined using the Virtual Phenotype system, or a variation thereof.

13. A method according to claim 1, that incorporates two or more of the methods recited in claims 5, 6, 8 and 9.

14. A method according to any one of the preceding claims which is a computer-implemented method.

15. A method according to claim 14, which is an automated method.

16. A method according to any one of the preceding claims, wherein the disease causing pathogen is obtained from a patient sample chosen from a blood sample, a biopsy sample, a plasma sample, a saliva sample, a tissue sample, and a bodily fluid or mucous sample.

17. A method according to any one of the preceding claims, wherein the disease causing pathogen is a virus.

18. A method according to claim 17, wherein the disease causing virus is chosen from HIV, HCV and HBV.

19. A method according to any one of the preceding claims, wherein the method is performed for a number of candidate drugs so as to provide information on the predicted fold resistance exhibited by the pathogen to a spectrum of candidate drugs.

20. A diagnostic method for optimising a drug therapy in a patient, comprising performing a method according to any one of the preceding claims for each drug or combination of drugs being considered to obtain a series of drug resistance phenotypes and therefore assess the effect of the plurality of drugs or drug combinations on the pathogen with which the patient is infected and selecting the drug or drug combination for which the pathogen is predicted to have the lowest fold resistance.

21. Use of a method according to any one of the preceding claims for assessing the efficiency of a patient's therapy or for evaluating or optimizing a therapy.

22. A diagnostic system for predicting clinical response to a drug of a disease causing pathogen comprising: a) means for obtaining a genetic sequence of the disease producing pathogen; b) means for identifying at least one mutation in the genetic sequence of the disease producing pathogen; c) genotype database means comprising genotype entries; d) phenotype database means comprising phenotypes of patient fold change response values; e) clinical response database means comprising clinical response to drug treatment for reference sample patients; f) correlation means correlating a genotype entry with a phenotype, where the genotype entry corresponds with the obtained genetic sequence of the disease producing pathogen; g) means for modelling clinical response to a drug of the disease causing pathogen by determining whether the patient fold change response

is above a cut-off value, wherein the cut-off value is determined using the clinical response database means and comprises the fold change response value at which a clinically relevant diminished clinical response is observed; and h) means for predicting the clinical response to a drug of a disease by determining whether the patient fold change response is above the cut-off value.

23. A diagnostic system according to claim 22, wherein the cut-off value is determined as a function of treatment response data in treated subjects, considering baseline pathogen load, baseline fold change resistance, baseline activity of co-administered drugs targeted to the pathogen and treatment history.

24. A computer apparatus or computer-based system adapted to perform the method of any one of claims 1-19.

25. A computer program product for use in conjunction with a computer, said computer program comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising a module that is configured so that upon receiving a request to predict the response of a disease caused by a pathogen to a drug it performs a method according to any one of claims 1-19.